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2) were obtained for the early onset families with total lod scores of -2.96, -2.51, -6.27, -5.81 and -10.95 with the markers *D14S52, D14S42, D14S43, D14S53* and *D14S55*, respectively. Significantly negative lod scores were also obtained for late onset families with these markers, and for the chromosome 21 marker in both early and late onset families (Table 1).

We can thus exclude linkage in these Swedish AD families to the reported region on chromosome 14 containing the putative AD gene for early onset disease, and to *APP* on chromosome 21. Genes other than the chromosome 14 gene and *APP* are thus involved in the aetiology of familial AD. This agrees with the finding that the Volga German pedigrees[11], and some other early-onset families[12,14], also show exclusion of both these loci. Our results strengthen the notion that familial AD has a heterogeneous aetiology.

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Nonsense mutations and diminished mRNA levels

Sir — Despite mounting evidence to the contrary, there is still a widespread belief that the predominant consequence of a premature termination codon (PTC) is the production of a truncated polypeptide[1–3]. In a majority of instances, the primary consequence of a PTC is a severe reduction in the level of mRNA from the mutant allele[4–6]. In model systems, a normal level of mutant transcript is only retained when the PTC is in the terminal exon or terminal-third of the penultimate exon. In most cases, mRNA containing a PTC is present at reduced levels in the cytoplasm and models have been proposed to explain this phenomenon[7]. In the "translational translocation" model, the translational machinery in the cytoplasm pulls the mRNA through the nuclear membrane. The "nuclear scanning" model predicts the existence of a means of scanning the mRNA for termination codons prior to translocation. The former model is more consistent with the observation that PTCs in the final exon allow translocation of mRNA and translation, whereas the latter more readily accommodates the observed skipping of constitutive exons containing termination codons[8]. It is possible that a combination of both may be employed and that neither is 100% effective, hence the small amounts of transcript observed *in vivo*[4–6,8].

In most cases, the level of protein produced from an allele containing a PTC has not been determined although a reduced amount would be expected due to the severe reduction in mRNA. The effect of PTCs (and truncated protein) might be expected to differ between dominant and recessive diseases. In recessive conditions the reduction in levels of normally functioning protein are probably sufficient to cause disease[4–6]. This may also be true for selected dominant disorders but in others a "dominant-negative" phenomenon may be involved. For example, in the Marfan syndrome, the greater the level of transcript from the null allele, the more severe the phenotype[8,9].

In the absence of evidence for the synthesis of significant amounts of a truncated protein, the predominant effect of nonsense mutations occurring prior to the penultimate exon should also be discussed in terms of reduction in the amount of transcript from the mutant allele.

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